Clinical Analysis of Adverse Drug Reactions

Karim Anton Calis, Pharm.D., M.P.H.
National Institutes of Health

March 12, 2009

Objectives

Define adverse drug reactions

Discuss epidemiology and classification of ADRs

Describe basic methods to detect, evaluate, and document ADRs

Definition

WHO

response to a drug that is *noxious and unintended* and that occurs at doses used in humans for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiologic function

excludes therapeutic failures, overdose, drug abuse, noncompliance, and medication errors

Adverse Drug Events

Adapted from Bates et al.

Graphic illustration showing a large circle entitled “Medication Errors (preventable)” with a smaller half-overlapping circle entitled “Adverse Drug Events (ME & ADR)”.

Adverse Drug Event: preventable or unpredicted medication event---with harm to patient

Epidemiology of ADRs

substantial morbidity and mortality

estimates of incidence vary with study methods, population, and ADR definition

4th to 6th leading cause of death among hospitalized patients*

6.7% incidence of serious ADRs*

0.3% to 7% of all hospital admissions

annual dollar costs in the billions

30% to 60% are preventable

***JAMA. 1998;279:1200-1205.**

Classification

Onset

Severity

Type

Classification

Onset of event:

Acute
- **within 60 minutes**

Sub-acute
- **1 to 24 hours**

Latent
- **> 2 days**

Classification - Severity

Severity of reaction:

Mild
- **bothersome but requires no change in therapy**

Moderate
- **requires change in therapy, additional treatment, hospitalization**

Severe
- **disabling or life-threatening**

Classification - Severity

FDA Serious ADR

- **Result in death**
- **Life-threatening**
- **Require hospitalization**
- **Prolong hospitalization**
- **Cause disability**
- **Cause congenital anomalies**
- **Require intervention to prevent permanent injury**

Classification

Type A

extension of pharmacologic effect

often predictable and dose dependent

responsible for at least two-thirds of ADRs

e.g., propranolol and heart block, anticholinergics and dry mouth

Classification

Type B

idiosyncratic or immunologic reactions

rare and unpredictable

e.g., chloramphenicol and aplastic anemia

Classification

Type C

associated with long-term use

involves dose accumulation

e.g., phenacetin and interstitial nephritis or antimalarials and ocular toxicity

Classification

Type D

delayed effects (dose independent)

Carcinogenicity (e.g., immunosuppressants)

Teratogenicity (e.g., fetal hydantoin syndrome)

Classification

Types of allergic reactions

Type I - immediate, anaphylactic (IgE)
e.g., anaphylaxis with penicillins

Type II - cytotoxic antibody (IgG, IgM)
e.g., methyldopa and hemolytic anemia

Type III - serum sickness (IgG, IgM)
Antigen-antibody complex
e.g., procainamide-induced lupus

Type IV - delayed hypersensitivity (T cell)
e.g., contact dermatitis

Classification – Type

Reportable

All significant or unusual adverse drug reactions as well as unanticipated or novel events that are suspected to be drug related

Classification – Type

Reportable

***Hypersensitivity**

Life-threatening

Cause disability

Idiosyncratic

Secondary to Drug interactions

Unexpected detrimental effect

Drug intolerance

Any ADR with investigational drug

Common Causes of ADRs

Antibiotics

Antineoplastics*

Anticoagulants

Cardiovascular drugs*

Hypoglycemics

Antihypertensives

NSAID/Analgesics

Diagnostic agents

CNS drugs*

***account for 69% of fatal ADRs**

Body Systems Commonly Involved

Hematologic

CNS

Dermatologic/Allergic

Metabolic

Cardiovascular

Gastrointestinal

Renal/Genitourinary

Respiratory

Sensory

ADR Risk Factors

Age (children and elderly)

Multiple medications

Multiple co-morbid conditions

Inappropriate medication prescribing, use, or monitoring

End-organ dysfunction

Altered physiology

Prior history of ADRs

Extent (dose) and duration of exposure

Genetic predisposition

ADR Frequency by Drug Use

Bar chart showing frequency (%) of ADRs by the number of medications a patient is taking from 0-5, 6-10, 11-15, and 16-20. As the number of medications a patient takes increases so does the frequency (%) of ADRs

May FE. Clin Pharmacol Ther 1977;22:322-8

ADR Detection

Subjective report
- patient complaint

Objective report:
- direct observation of event
- abnormal findings
  - physical exam
  - laboratory test
  - diagnostic procedure

ADR Detection

Medication order screening

- abrupt medication discontinuation
- abrupt dosage reduction
- orders for “tracer” or “trigger” substances
- orders for special tests or serum drug concentrations

Spontaneous reporting

Medication utilization review

- Computerized screening
- Chart review and concurrent audits

ADR Detection in Clinical Trials

Methods

Standard laboratory tests

Diagnostic tests

Complete history and physical

Adverse drug event questionnaire

- Extensive checklist of symptoms categorized by body system
- Review-of-systems approach
- Qualitative and quantitative

ADR Detection in Clinical Trials

Limitations

- **exposure limited to few individuals**
  - **rare and unusual ADRs not detected**
  - **3000 patients at risk are needed to detect ADR with incidence of 1/1000 with 95% certainty**
- **exposure is often short-term**
  - **latent ADRs missed**
- **external validity**
  - **may exclude children, elderly, women of child-bearing age; and patients with severe form of disease, multiple co-morbidities, and those taking multiple medications**

Preliminary Assessment

Preliminary description of event:

Who, what, when, where, how?

***Who* is involved?**

***What* is the most likely causative agent?**

- **Is this an exacerbation of a pre-existing condition?**
- **Alternative explanations / differential diagnosis**

***When* did the event take place?**

***Where* did the event occur?**

***How* has the event been managed thus far?**

Preliminary Assessment

Determination of urgency:

What is the patient's current clinical status?
How severe is the reaction?

Appropriate triage:

Acute (ER, ICU, Poison Control)

Detailed Description of Event PQRSTA Acronym

Electrocardiogram tracing with P wave, QRS complex and T wave.

Detailed Description of Event

History of present illness

Signs / Symptoms: PQRSTA

Provoking or palliative factors

Quality (character or intensity)

Response to treatment, Radiation, Reports in literature

Severity / extent, Site (location)

Temporal relationship (onset, duration, frequency)

Associated signs and symptoms

Pertinent Patient/Disease Factors

Demographics

age, race, ethnicity, gender, height, weight

Medical history and physical exam

Concurrent conditions or special circumstances

e.g., dehydration, autoimmune condition, HIV infection, pregnancy, dialysis, breast feeding

Recent procedures or surgeries and any resultant complications

e.g., contrast material, radiation treatment, hypotension, shock, renal insufficiency

Pertinent Patient/Disease Factors

End-organ function

Review of systems

Laboratory tests and diagnostics

Social history
- **tobacco, alcohol, substance abuse, physical activity, environmental or occupational hazards or exposures**

Pertinent family history

Nutritional status
- **special diets, malnutrition, weight loss**

Pertinent Medication Factors

Medication history

- **Prescription medications**
- **Non-prescription medications**
- **Alternative and investigational therapies**
- **Medication use within previous 6 months**
- **Allergies or intolerances**
- **History of medication reactions**
- **Adherence to prescribed regimens**
- **Cumulative mediation dosages**

Pertinent Medication Factors

Medication
- Indication, dose, diluent, volume

Administration
- Route, method, site, schedule, rate, duration

Formulation
- Pharmaceutical excipients
  - e.g., colorings, flavorings, preservatives
- Other components
  - e.g., DEHP, latex

Pertinent Medication Factors

- **Pharmacology**
- **Pharmacokinetics (LADME)**
- **Pharmacodynamics**
- **Adverse effect profiles**
- **Interactions**
  - **drug-drug**
  - **drug-nutrient**
  - **drug-lab test interference**

Cross-allergenicity or cross-reactivity

ADR Information

Incidence and prevalence

Mechanism and pathogenesis

Clinical presentation and diagnosis

Time course

Dose relationship

Reversibility

Cross-reactivity/Cross-allergenicity

Treatment and prognosis

ADR Information Resources

Tertiary

Reference books

Medical and pharmacotherapy textbooks

Package inserts, PDR, AHFS, USPDI

Specialized ADR resources
- **Meyler's Side Effects of Drugs**
- **Textbook of Adverse Drug Reactions**

Drug interactions resources

Micromedex databases (e.g., TOMES, POISINDEX, DRUGDEX)

Review articles

ADR Information Resources

Secondary

MEDLARS databases (e.g., Medline, Toxline, Cancerline, Toxnet)

Excerpta Medica's Embase

International Pharmaceutical Abstracts

Current Contents

Biological Abstracts (Biosis)

Science Citation Index

Clin-Alert and Reactions

ADR Information Resources

Primary

Spontaneous reports or unpublished data

FDA

Manufacturer

Anecdotal and descriptive reports

Case reports, case series

Observational studies

Case-control, cross-sectional, cohort

Experimental and other studies

Clinical trials

Meta-analyses

Causality Assessment

Prior reports of reaction

Temporal relationship

De-challenge

Re-challenge

Dose-response relationship

Alternative etiologies

Objective confirmation

Past history of reaction to same or similar medication

Causality Assessment

Examples of causality algorithms

- **Kramer**
- **Naranjo and Jones**

Causality outcomes

- **Highly probable**
- **Probable**
- **Possible**
- **Doubtful**

Naranjo ADR Probability Scale

This is a copy of the Naranjo ADR Probably Scale Questionnaire which is used to access an adverse drug reaction by completing the questionnaire and giving the appropriate score.

Total Score	ADR Probability Classification
9	Highly probably
5-8	Probable
1-4	Possible
0	Doubtful

Naranjo CA. Clin Pharmacol Ther 1981;30:239-45

Management Options

Discontinue the offending agent if:

it can be safely stopped

the event is life-threatening or intolerable

there is a reasonable alternative

continuing the medication will further exacerbate the patient's condition

Continue the medication (modified as needed) if:

it is medically necessary

there is no reasonable alternative

the problem is mild and will resolve with time

Management Options

Discontinue non-essential medications

Administer appropriate treatment

e.g., atropine, benztropine, dextrose, antihistamines, epinephrine, naloxone, phenytoin, phytonadione, protamine, sodium polystyrene sulfonate, digibind, flumazenil, corticosteroids, glucagon

Provide supportive or palliative care

e.g., hydration, glucocorticoids, warm / cold compresses, analgesics or antipruritics

Consider rechallenge or desensitization

Follow-up and Re-evaluation

Patient's progress

Course of event

Delayed reactions

Response to treatment

Specific monitoring parameters

Documentation and Reporting

Medical record

Description

Management

Outcome

Reporting responsibility

JCAHO-mandated reporting programs

Food and Drug Administration

post-marketing surveillance

particular interest in serious reactions involving new chemical entities

Pharmaceutical manufacturers

Publishing in the medical literature

Components of an ADR Report

Product name and manufacturer

Patient demographics

Description of adverse event and outcome

Date of onset

Drug start and stop dates/times

Dose, frequency, and method

Relevant lab test results or other objective evidence

De-challenge and re-challenge information

Confounding variables

MEDWATCH 3500A Reporting Form

This is the FDA Medical Products Reporting Program

For use by user-facilities, distributors and manufacturers for MANDATORY reporting.

https://www.accessdata. fda.gov/scripts/medwatch